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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Paul Alexander JONES et al.
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HEREWITH
INTERNATIONAL APPLICATION NO.: PCT/GB00/02788
INTERNATIONAL FILING DATE: July 19, 2000
FOR: NEW USE OF A MACROLIDE COMPOUND

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO	DAY/MONTH/YEAR
Great Britain	9917158.9	21 July 1999

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/GB00/02788.

Respectfully submitted,
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PCT/GB00/02788

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RECT 10 AUG 2000

PRIORITY DOCUMENT

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4

GB00/02788

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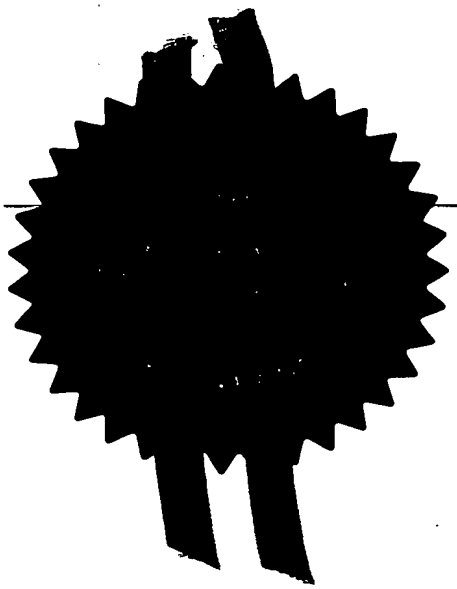

Signed Andrew Gorvey

Dated 27 JUL 2000

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Act 1977

The Patent Office

21JUL99 E463884-3 C03077
P01/0.00 - 9917158.9

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Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
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1. Your reference

RJG/1797 GB

21 JUL 1999

2. Patent application number
(The Patent Office will fill in this part)

9917158.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

FUJISAWA PHARMACEUTICAL CO., LTD.
4-7 DOSHOMACHI 3-CHOME
CHUO-KU
OSAKA-SHI
OSAKA 541-8514
JAPAN

Patents ADP number *(if you know it)*

5894282001

If the applicant is a corporate body, give the country/state of its incorporation

JAPAN

4. Title of the invention

NEW USE

5. Name of your agent *(if you have one)*

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UNITED KINGDOM

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)*

1545003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Description	5
Claim(s)	1
Abstract	1
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request ~~the~~ grant of a patent on the basis of this application.

Signature Stevens, Hewlett & Perkins Date 21.7.1999

STEVENS, HEWLETT & PERKINS

12. Name and daytime telephone number of person to contact in the United Kingdom: R GAUNT 0171 936 2499

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Notes

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DESCRIPTION

NEW USE

TECHNICAL FIELD

This invention relates to a new use of a macrolide compound.

BACKGROUND ART

A certain macrolide compound, i.e., tacrolimus, and its related compounds are known to have preventing or treating activity of cerebral infarction (USP 5,648,351). However, it is desirable to provide more effective and/or safer drug with a superior pharmaceutical profile against cerebral ischemic disease.

DISCLOSURE OF INVENTION

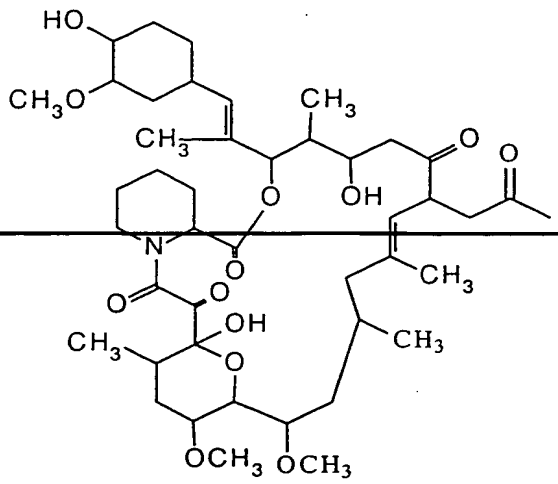
The inventors of this invention have found that one of the tacrolimus analogues, i.e., a compound (I), mentioned below, has an excellent neuroprotective efficacy.

Accordingly, this invention provides a new use of the compound (I) as a neuroprotective agent.

Further, this invention provides a neuroprotective agent, which comprises the compound (I).

Still further, this invention provides a method for preventing or treating acute or chronic cerebral neurodegenerative diseases, which comprises administering said compound (I) to mammals.

The tacrolimus analogue used in the present invention has the following chemical formula.



(I)

It has already been produced in USP 5,376,663,example 29.

With respect to the compound (I) used in the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double bond(s), and such conformers and isomers are also included within the scope of the compound in the present invention. And further, the compound can be in the form of a solvate or pro-drug, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

The compound (I) usable in the present invention may be administered as pure compound or mixture of compound or preferably, in a pharmaceutical vehicle or carrier.

The compound (I) in this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the compound(I), as an active ingredient, in admixture with an organic or inorganic

carrier or excipient suitable for external(topical), enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, eye drops, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), ointment, aerosol sprays, cream, skin plasters, patches and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

For applying this composition to a human, it is preferable to apply it by injection.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.0001-1000 mg, preferably 0.001-500 mg and more preferably 0.01-100 mg. of the active ingredient is generally given for treating diseases, and an average single dose of about 0.001-0.01mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100

mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.1-30 mg/kg/day.

And further, the compound (I) can be applied, simultaneously, separately or sequentially, with other agents having neuroprotective activity, and so on.

The following examples illustrate the present invention in further detail. It should be understood that those examples are not intended to limit the scope of the invention.

Example 1

Neuroprotective efficacy of the compound (I) in the rat endothelin-induced MCA occlusion model

(1) METHOD

The compound (I) was dissolved in a polyoxyethylene-hydrogenated castor oil 60/ethanol (400mg/1ml) solution and administered at 1 and 3 $mg.kg^{-1}$. All drugs and relevant control were administered in a volume of 2 $ml.kg^{-1}$. MCA occlusion by the endothelin method was performed on male Sprague Dawley rats (271 - 324g) as described in USP 5,648,351. All drugs were infused through the i.v. catheter at 1 ml min^{-1}, five minutes post-lesion. The animals were sacrificed by cardiac infusion under barbital anaesthesia. Volume of lesion was calculated from measured areas of damage (as assessed three days post-lesion) using the Trapezoid Rule. Results are presented as volume (mm^3) $\pm$ SEM. Statistical analysis was performed using ANOVA and post hoc Student-Newman-Keuls test, where $p < 0.05$ was set as an acceptable level for significance.

(2) RESULT

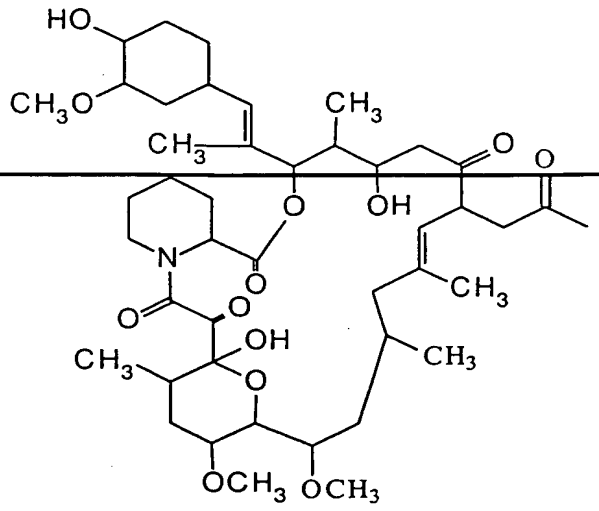
Protection in the ET-1 model of stroke by the compound (I) at 1 $mg.kg^{-1}$ (n=14) and 3 $mg.kg^{-1}$ (n=9) against vehicle (n=11) was studied. The compound (I) protected the cortex 61% and 42% respectively at both 1 and 3 $mg.kg^{-1}$.

The compound (I) was proved to have a neuroprotective efficacy. So, the present invention provides useful neuroprotective agent for preventing or treating acute or chronic cerebral neurodegenerative diseases, such as cerebral ischemic diseases and/or brain damage caused by ischemia. So, it is useful when the following diseases or injury occur, that is, cerebral infarction, head injury, hemorrhage in brain such as subarachnoid hemorrhage or intracerebral hemorrhage, cerebral thrombosis, cerebral embolism, cardiac arrest, stroke (such as acute stroke), transient ischemic attacks (TIA), hypertensive encephalopathy, Alzheimer's disease, Huntington's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and so on.

The patents, patent applications and publications cited herein are incorporated by reference.

CLAIMS

1. A use of a compound of the following formula:



(I)

for manufacturing an neuroprotective agent.

2. A method for preventing or treating acute or chronic cerebral neurodegenerative diseases, which comprises administering the compound (I) identified in Claim 1 to mammals.

3. A pharmaceutical composition for preventing or treating acute or chronic cerebral neurodegenerative diseases, which comprises compound (I) in admixture with a carrier or excipient.

4. A use of the compound (I) for preventing or treating acute or chronic cerebral neurodegenerative diseases.

5. The acute or chronic cerebral neurodegenerative diseases in Claims 1 to 4 is cerebral infarction.

ABSTRACT

Macrolide compound, such as a tacrolimus analogue is provided for use as a neuroprotective agent, particularly, for preventing or treating acute or chronic cerebral neurodegenerative diseases.